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Synthesis of the Oxepinochromone Natural Products Ptaeroxylin (Desoxykarenin), Ptaeroxylinol, and Eranthin

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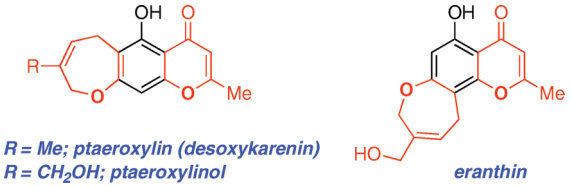

An improved synthesis of the oxepinochromone ptaeroxylin is reported, together with the syntheses of the related natural products ptaeroxylinol and eranthin. Ptaeroxylin and ptaeroxylinol were obtained from the chromenone noreugenin by selective reaction of the 7-hydroxyl group, allylation of the 5-hydroxyl, followed by Claisen rearrangement under microwave conditions with concomitant deprotection of the 7-hydroxyl. Alkylation of the 7-hydroxyl with the appropriate allyl bromide provides a precursor for ring-closing metathesis to deliver the oxepinochromone ring system. Eranthin was obtained by a similar strategy involving Claisen rearrangement to transfer an allyl group from the C-7 hydroxyl of noreugenin to C-8 regioselectively.

Introduction

The benz[*b*]oxepine ring system occurs in a small number of biologically active natural products isolated mainly from plant sources. Some examples are shown in Figure 1 and include the radulanins **1**−**3** and heliannuols, exemplified by heliannuol D (**4**), isolated from liverwort and sunflowers, respectively, and the subject of a number of successful syntheses,[1−8] and pterulone (**5**) and pterulinic acid (**6**), isolated from a *Pterula* fungus,[9,10] both of which have also been synthesized.[11−13]

Much less well-known are the sneezewood derived oxepino[3,2-*g*]chromones ptaeroxylin (**7**), karenin (**8**), and ptaeroxylinol (**9**),[14−16] and the isomeric oxepinochromone eranthin (**10**), isolated from *Eranthis hiemalis*.[17] Trees of the *Ptaeroxylon* genus produce extremely durable timber, although the sawdust apparently causes violent sneezing; hence, the tree is more commonly known as sneezewood. The constituents of *Ptaeroxylon obliquum* were investigated independently in the 1960s by two research groups, and this led to the isolation of a number of novel chromones upon extraction of the heartwood.[14−16] The first of these, named ptaeroxylin, was originally assigned an angular oxepino[2,3-*h*]chromone structure (cf. eranthin **10**),[14] but following its reisolation by the second research group, the compound was reassigned the linear oxepino[3,2-*g*]chromone structure **7** and given the

(1) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808.
(2) Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **2000**, *41*, 4787.
(3) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505.
(4) Yoshida, M.; Nakatani, K.; Shishido, K. *Tetrahedron* **2009**, *65*, 5702.
(5) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807.
(6) Macias, F. A.; Chinchilla, D.; Molinillo, J. M. G.; Marin, D.; Varela, R. M.; Torres, A. *Tetrahedron* **2003**, *59*, 1679.
(7) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 983.
(8) Vyvyan, J. R.; Oaksmith, J. M.; Parks, B. W.; Peterson, E. M. *Tetrahedron Lett.* **2005**, *46*, 2457.
(9) Engler, M.; Anke, T.; Sterner, O.; Brandt, U. *J. Antibiot.* **1997**, *50*, 325.
(10) Engler, M.; Anke, T.; Sterner, O. *J. Antibiot.* **1997**, *50*, 330.
(11) Huang, S. T.; Kuo, H. S.; Chen, C. T. *Tetrahedron Lett.* **2001**, *42*, 7473.
(12) Lin, Y. L.; Kuo, H. S.; Wang, Y. W.; Huang, S. T. *Tetrahedron* **2003**, *59*, 1277.
(13) Lemaire, P.; Balme, G.; Desbordes, P.; Vors, J. P. *Org. Biomol. Chem.* **2003**, *1*, 4209.
(14) Dean, F. M.; Taylor, D. A. H. *J. Chem. Soc. C* **1966**, 114.
(15) McCabe, P. H.; McCrindle, R.; Murray, R. D. H. *J. Chem. Soc. C* **1967**, 145.
(16) Dean, F. M.; Parton, B.; Somvichien, N.; Taylor, D. A. H. *Tetrahedron Lett.* **1967**, 3459.
(17) Junior, P. *Phytochemistry* **1979**, *18*, 2053.

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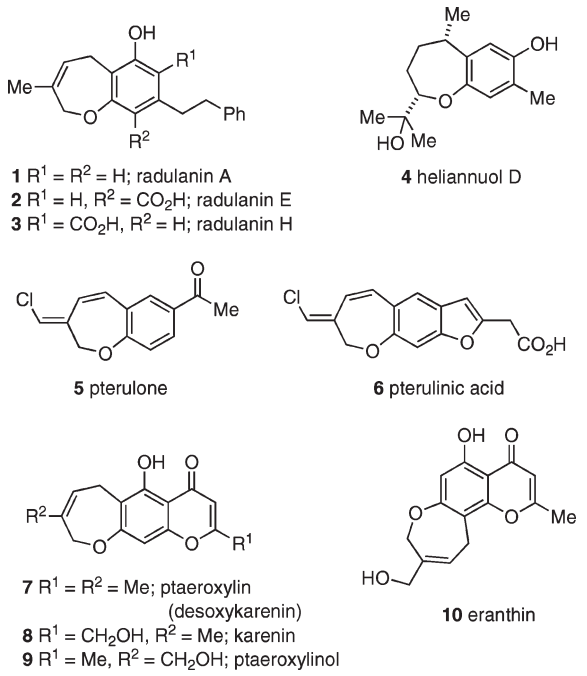


FIGURE 1. Some naturally occurring benzoxepines.

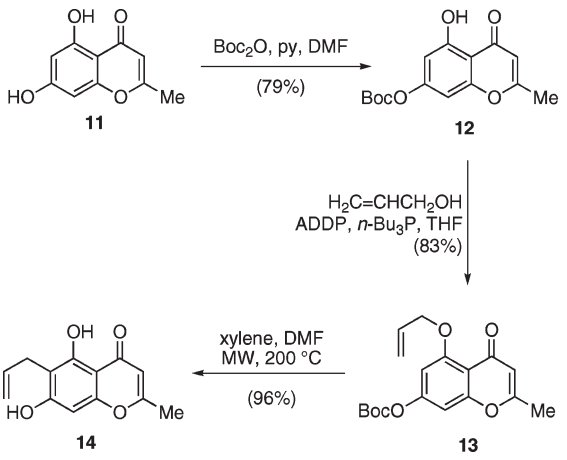
name desoxykarenin, karenin (**8**) being isolated from the same source.[15] Ptaeroxylinol (**9**), isomeric with karenin, was subsequently isolated from the tree (Figure 1).[16] Eranthin (**10**) was isolated along with its β-D-glucoside a decade later and with the advantage of more sophisticated NMR instrumentation was assigned the angular oxepinochromone structure.[17] Other glycoside derivatives have also been isolated.[18]

Despite their relative structural simplicity, aside of our own preliminary report on ptaeroxylin (**7**),[19] there has been no synthetic work on this family of natural products. In view of the paucity of spectroscopic data in the early papers from the 1960s, and the ensuing structural uncertainty, we decided to resolve the issue by synthesis. We now describe the first syntheses of ptaeroxylinol (**9**) and the isomeric oxepinochromone eranthin (**10**), together with details of an earlier synthesis of ptaeroxylin (**7**).

Results and Discussion

Although we have previously developed a route to benzoxepine derivatives based on intramolecular carbene O−H insertion reactions,[20,21] our plan in this case was to form the 7-membered oxygen heterocycle of the oxepinochromones by ring-closing metathesis (RCM), a reaction that has rapidly gained acceptance as a key tactic in the construction of a wide range of carbo- and heterocyclic ring systems and that has found use in the synthesis of benzo-fused medium ring ethers.[1,22,23] Therefore, a relatively simple chromone derivative **14** was required as a key intermediate (Scheme 1). The starting material, 5,7-dihydroxy-2-methylchromen-4-one (**11**), is a

SCHEME 1



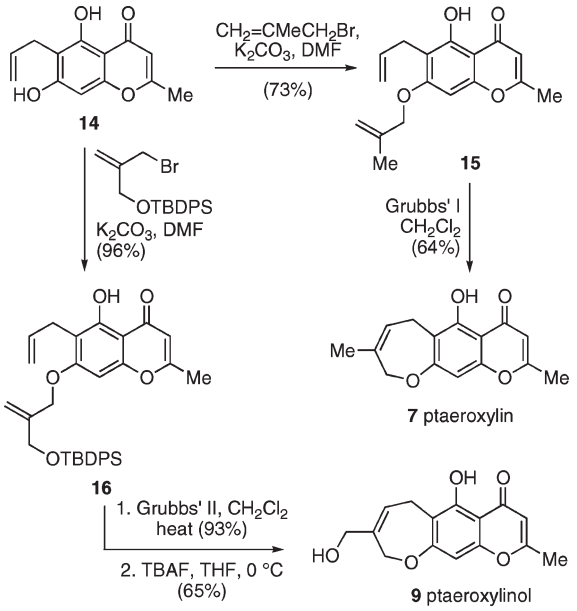
natural product itself known as noreugenin[24] and was readily prepared using the Kostanecki−Robinson synthesis from 2,4,6-trihydroxyacetophenone based on a literature protocol,[25,26] although we found that microwave heating gave better yields. Our original conversion of noreugenin into chromenone **14** was somewhat cumbersome,[19] but we have now much improved this sequence simply by changing the phenolic protecting group from methoxymethyl to *tert*-butoxycarbonyl. Thus, selective protection of the non-hydrogen-bonded phenol in noreugenin (**11**) gave the monocarbonate **12**, and subsequent Mitsunobu reaction with allyl alcohol, azodicarbonyl dipiperidine (ADDP), and tri-*n*-butylphosphine delivered the Claisen rearrangement substrate **13** in high yield. Heating allyl ether **13** to 200 °C in a microwave reactor resulted in the desired Claisen rearrangement with concomitant cleavage of the Boc group[27] to give the chromone **14** (Scheme 1) in three steps in 63% yield, compared with 32% over five steps in our original route.[19]

The synthesis of ptaeroxylin (**7**) was completed by a selective alkylation of the C-7 hydroxy group in chromone **14** with 3-bromo-2-methylpropene to give the methallyl ether **15**, the substrate for the RCM reaction. Treatment of the precursor **15** with bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs' I catalyst) resulted in formation of the desired 7-membered ring **7** in good yield (Scheme 2). Although one must exercise caution in comparing spectroscopic data from over 40 years ago, the melting point, ^{1}H NMR, IR, and UV data quoted for the natural product[14,15] very closely matched those for our synthetic sample,[19] leading us to conclude that they are the same compound.

Similar methodology was then used to complete the first synthesis of ptaeroxylinol (**9**) (Scheme 2). Initially we used either 3-bromo-2-(*tert*-butyldimethylsiloxy)methylpropene or 3-bromo-2-(acetoxymethyl)propene to alkylate the C-7 phenol in chromone **14**, but owing to unsatisfactory yields, we settled for the more stable 3-bromo-2-(*tert*-butyldiphenylsiloxy)methylpropene, readily prepared in two steps

(18) Kopp, B.; Kubelka, E.; Reich, C.; Robien, W.; Kubelka, W. *Helv. Chim. Acta* **1991**, *74*, 611.
(19) Muscarella, M.; Kimber, M. C.; Moody, C. J. *Synlett* **2008**, 2101.
(20) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.
(21) Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721.
(22) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(23) Chattopadhyay, S. K.; Biswas, T.; Maity, S. *Synlett* **2006**, 2211.
(24) Brown, R. T.; Blackstock, W. P.; Chapple, C. L. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1776.
(25) Murti, V. V. S.; Seshadri, T. R. *Proc. Ind. Acad. Sci., Sect. A* **1949**, *30A*, 107.
(26) Rehder, K. S.; Kepler, J. A. *Synth. Commun.* **1996**, *26*, 4005.
(27) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7501.

SCHEME 2

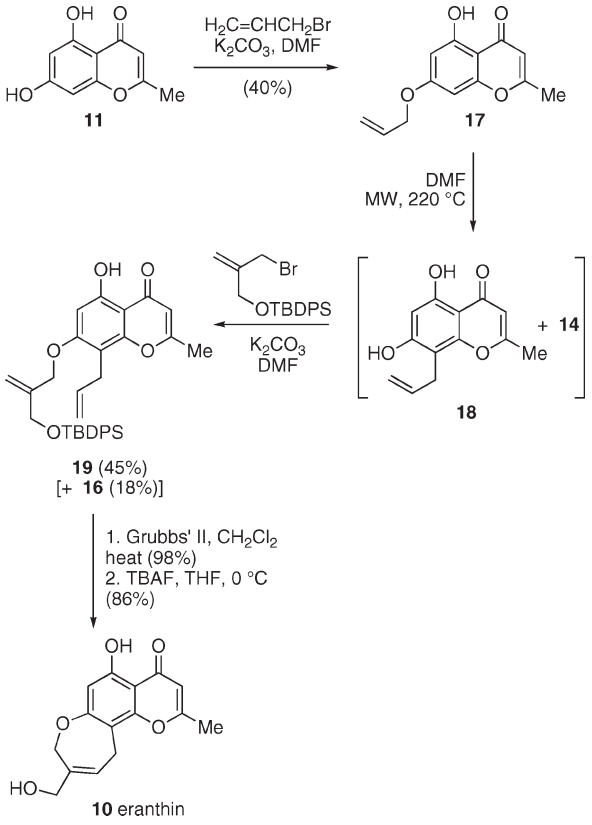


by monosilylation of 2-methylenepropane-1,3-diol, followed by treatment with phosphorus tribromide. The alkylation step proceeded smoothly and gave the RCM precursor **16** in excellent yield, which was treated with [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene](tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs' II catalyst), the presence of the bulky silyl protecting group dictating the use of a catalyst better suited for the metathesis of sterically demanding olefins. This resulted in formation of the desired 7-membered ring, again in excellent yield. Finally, removal of the silicon protecting group delivered ptaeroxylinol (**9**) (Scheme 2). The structure of the synthetic material **9** was unambiguously confirmed by X-ray crystallography (see the Supporting Information), and although there is far too little NMR spectroscopic data reported for the natural product to make a sensible comparison,[16] the close resemblance of the ^{1}H NMR data for our synthetic ptaeroxylinol (**9**) and for natural ptaeroxylin (**7**)[14,15] suggest that the structures of the two natural products are very similar. In addition, the IR data for the synthetic material closely match those reported for the natural product,[28] and hence we assume that ptaeroxylinol (**9**) does indeed have the indicated structure.

With the Claisen rearrangement−RCM protocol now well established a short synthesis of eranthin (**10**) was possible. This compound isolated from the winter aconite *Eranthis hiemalis*[17] has not been synthesized to date. Selective allylation of noreugenin (**11**) at the 7-hydroxy group was achieved in modest yield, and this was followed by heating the resulting allyl ether **17** in DMF to effect the Claisen rearrangement. On the basis of previous work on the rearrangement of related 7-allyloxyflavones that proceeded regioselectively to the 8-position,[29] we expected the 7-allyloxychromone to behave similarly. In the event, the Claisen rearrangement was disappointingly unselective and gave a mixture of the desired 8-allyl compound **18** and the 6-allyl isomer **14**

(28) Epe, B.; Oelbermann, U.; Mondon, A. *Chem. Ber.* **1981**, *114*, 757.
(29) Moody, C. J. *Adv. Heterocycl. Chem.* **1987**, *42*, 203.

SCHEME 3



(ratio = 2.5:1). The isomers were not separated at this stage but were alkylated with 3-bromo-2-(*tert*-butyldiphenylsiloxy)methylpropene to give the required RCM precursor **19** (45% over two steps) together with the isomeric compound **16** (18%) (Scheme 3). Treatment of compound **19** with Grubbs' second-generation catalyst delivered the oxepinochromone in excellent yield, deprotection of which completed the first synthesis of eranthin (**10**). Again, the structure of our synthetic material **10** was unambiguously confirmed by X-ray crystallography (see the Supporting Information), and since the ^{1}H and ^{13}C NMR spectroscopic data of the synthetic sample very closely matched those reported for the natural product,[17] we conclude that eranthin has the assigned structure.

In summary, we have used a combined Claisen rearrangement − RCM strategy to provide efficient access to naturally occurring oxepinochromones, two of which (ptaeroxylinol and eranthin) have been synthesized for the first time, thereby confirming their structures.

Experimental Section

5,7-Dihydroxy-2-methyl-4*H*-chromen-4-one (Noreugenin, 11). A mixture of 2,4,6-trihydroxyacetophenone (3.0 g, 16.11 mmol) and sodium acetate (1.32 g, 16.11 mmol) in acetic anhydride (8.06 mL) was heated at 180 °C for 40 min in a microwave reactor (300 W). The reaction mixture was kept warm, added dropwise to cold water (50 mL), and filtered. The resulting solid was added to a boiling aqueous potassium carbonate solution (0.1 M; 160 mL) and further heated at reflux for 2 h. The mixture was cooled to 0 °C and acidified with concentrated hydrochloric acid (5 mL). The product that precipitated was filtered and washed with aqueous hydrochloric acid (10%) and dried in

vacuo over potassium hydroxide to give a beige powder (1.80 g, 59%): mp >230 °C (lit.[25] mp 279−280 °C; lit.[24] mp 275−280 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3630, 2930, 1618, 1503, 1450, 1365, 1289, 1124; δ_H (400 MHz; DMSO-d_6) 12.80 (1 H, s), 10.78 (1 H, s), 6.30 (1 H, d, J = 2.0), 6.16 (1 H, d, J = 2.0), 6.13 (1 H, s), 2.32 (3 H, s); δ_C (100 MHz; DMSO-d_6) 181.7 (C), 167.5 (C), 164.0 (C), 161.5 (C), 157.7 (C), 107.9 (CH), 103.4 (C), 98.7 (CH), 93.64 (CH), 19.8 (Me); HRMS calcd for $C_{10}H_8O_4 + Na^+$ 215.0315, found MNa^+ 215.0308.

***tert*-Butyl 5-Hydroxy-2-methyl-4-oxo-4*H*-chromen-7-yl Carbonate 12.** To a solution of noreugenin (**11**) (1.0 g, 5.21 mmol) in DMF (17 mL) were added pyridine (0.63 mL, 7.81 mmol) and di-*tert*-butyl dicarbonate (1.41 g, 6.25 mmol) at 0 °C under argon. The reaction mixture was stirred for 16 h at room temperature and slowly quenched with cold saturated aqueous ammonium chloride (25 mL). The mixture was extracted into ethyl acetate (2 × 30 mL) and the organic layer washed with brine (3 × 30 mL), dried over magnesium sulfate, filtered, and evaporated in vacuo. The resulting oil was purified by chromatography (light petroleum/ether, 65:35) to give the title compound (1.52 g, 79%) as a colorless oil: ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 2986, 1762, 1661, 1628, 1599, 1413, 1252, 1135, 1078, 851; δ_H (400 MHz; $CDCl_3$) 12.67 (1 H, s), 6.76 (1 H, d, J = 2.1), 6.61 (1 H, d, J = 2.1), 6.08 (1 H, s), 2.36 (3 H, s), 1.56 (9 H, s); δ_C (100 MHz; $CDCl_3$) 182.7 (C), 167.6 (C), 161.8 (C), 157.0 (C), 156.0 (C), 150.5 (CH), 109.1 (CH), 108.3 (C), 104.8 (CH), 100.2 (CH), 84.5 (C), 27.6 (Me), 20.5 (Me); HRMS calcd for $C_{15}H_{16}O_6 + Na^+$ 315.0839, found MNa^+ 315.0833.

5-Allyloxy-2-methyl-4-oxo-4*H*-chromen-7-yl *tert*-Butyl Carbonate (13). To a mixture of **12** (1.19 g, 4.05 mmol), allyl alcohol (0.41 mL, 6.08 mmol) and 1,1′-(azodicarbonyl)-dipiperidine (2.05 g, 8.11 mmol) in THF (14 mL) was added tri*n*-butyl phosphine (2.03 mL, 8.11 mmol) at 0 °C under argon. The reaction mixture was stirred for 16 h at room temperature, diluted with ether (20 mL), cooled to 4 °C, and filtered. The filtrate was reduced in vacuo and the resulting oil purified by chromatography (light petroleum/ethyl acetate, 1:1) to give the title compound (1.12 g, 83%) as colorless crystals: mp 97−99 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1762, 1659, 1613, 1480, 1429, 1394, 1372, 1336, 1251, 1137, 1088, 991, 871; δ_H (400 MHz; $CDCl_3$) 6.88 (1 H, d, J = 2.2), 6.60 (1 H, d, J = 2.2), 6.08 (1 H, ddt, J = 17.2, 10.6, 4.7), 6.02 (1 H, s), 5.66 (1 H, ddt, J = 17.2, 1.6, 1.7), 5.34 (1 H, ddt, J = 10.6, 1.7, 1.5), 4.65 (2 H, dt, J = 4.7, 1.7), 2.27 (3 H, s), 1.56 (9 H, s); δ_C (100 MHz; $CDCl_3$) 177.0 (C), 163.5 (C), 159.5 (C), 158.8 (C), 154.4 (C), 150.5 (C), 131.8 (CH), 118.0 (CH_2), 112.3 (C), 112.1 (CH), 102.5 (CH), 101.7 (CH), 84.5 (C), 69.9 (CH_2), 27.6 (Me), 19.8 (Me); HRMS calcd for $C_{18}H_{20}O_6 + Na^+$ 355.1152, found MNa^+ 355.1154.

6-Allyl-5,7-dihydroxy-2-methyl-4*H*-chromen-4-one (14). A solution of **13** (500 mg, 1.50 mmol) in a xylene/DMF mixture (95:5) (25 mL) was heated at 200 °C for 90 min in a microwave reactor (300 W). The reaction mixture was concentrated, taken up in aqueous potassium hydroxide solution (10%; 25 mL) at 0 °C, and then acidified with concentrated hydrochloric acid (3 mL). The product that precipitated was filtered, washed with aqueous hydrochloric acid (10%), and dried in vacuo over potassium hydroxide to give a beige solid (326 mg, 93%): mp 232−234 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3585, 3011, 1657, 1630, 1590, 1492, 1457, 1416, 1349, 1277, 1190, 849; δ_H (400 MHz; DMSO-d_6) 13.07 (1 H, s), 10.87 (1 H, s), 6.46 (1 H, s), 6.14 (1 H, s), 5.86 (1 H, ddt, J = 16.9, 10.3, 5.6), 4.96−4.90 (2 H, m), 3.25 (2 H, d, J = 5.6), 2.33 (3 H, s); δ_C (100 MHz; d_6-DMSO) 182.7 (C), 168.2 (C), 162.8 (C), 159.6 (C), 156.7 (C), 136.7 (CH), 115.5 (CH_2), 109.8 (C), 108.7 (CH), 104.0 (C), 93.9 (CH), 26.9 (CH_2), 20.8 (Me); HRMS calcd for $C_{13}H_{12}O_4 + Na^+$ 255.0628, found MNa^+, 255.0627.

6-Allyl-5-hydroxy-2-methyl-7-(2-methylprop-2-en-1-yl)oxy-4*H*-chromen-4-one (15). To a solution of 6-allyl-5,7-dihydroxy-2-methyl-4*H*-chromen-4-one **14** (0.09 g, 0.39 mmol) in DMF (1.3 mL) were added potassium carbonate (0.07 g, 0.07 mmol) and 3-bromo-2-methyl-1-propene (0.05 mL, 0.43 mmol). The mixture was stirred for 1.5 h, quenched with water (10 mL), and acidified with hydrochloric acid (6 M). The resulting product was filtered, washed, and dried to give the title compound as a colorless solid (0.08 g, 73%): mp 62−64 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1660, 1625, 1591, 1490, 1450, 1343, 1186, 1134; δ (400 MHz; $CDCl_3$) 12.81 (1 H, s), 6.34 (1 H, s), 6.02 (1 H, s), 6.01−5.91 (1 H, m), 5.11−4.95 (4 H, m), 4.48 (2 H, s), 3.45 (2 H, d, J = 6.4), 2.34 (3 H, s), 1.84 (3 H, s); δ (100 MHz; $CDCl_3$) 182.4 (C), 166.4 (C), 162.0 (C), 158.7 (C), 156.6 (C), 139.9 (C), 135.8 (CH), 114.6 (CH_2), 113.0 (CH_2), 111.1 (C), 108.8 (CH), 105.1 (C), 90.4 (CH), 72.0 (CH_2), 26.5 (CH_2), 20.4 (Me), 19.3 (Me); HRMS calcd for $C_{17}H_{18}O_4$ + H 287.1278, found MH^+ 287.1275.

5-Hydroxy-6,9-dihydro-2,8-dimethyl-4*H*-oxepino[3,2-*g*]chromen-4-one (Ptaeroxylin, 7). A solution of 6-allyl-5-hydroxy-2-methyl-7-[(2-methylprop-2-en-1-yl)oxy]-4*H*-chromen-4-one (**15**) (0.035 g, 0.135 mmol) in dichloromethane (65 mL, 0.002 M) was treated with a single portion (0.021 g, 20 mol %) of bis-(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride. The solution was heated under reflux for 18 h. The solvent was removed in vacuo, and the brown residue was filtered through a short pad of Celite using cyclohexane/ethyl acetate (9:1) as eluent. The solvent was then removed and the residue purified by chromatography (cyclohexane/ethyl acetate, 9:1) to give the title compound as a colorless solid (0.020 g, 64%): mp 126−128 °C (lit.[15] mp 133−135 °C); λ_{max} (MeCN)/nm 232 (log ε 4.2), 254 (4.1), 322 (3.5); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1655, 1626, 1592, 1449, 1406; δ (400 MHz; $CDCl_3$) 13.00 (1 H, s), 6.54 (1 H, s), 6.04 (1 H, s), 5.71−5.68 (1 H, br t, J = 4.4), 4.51 (2 H, s), 3.48 (2 H, d, J = 4.4), 2.35 (3 H, s), 1.60 (3 H, s); δ (100 MHz; $CDCl_3$) 182.8 (C), 167.0 (C), 164.5 (C), 157.6 (C), 155.8 (C), 133.6 (C), 121.8 (CH), 117.9 (C), 108.7 (CH), 106.9 (C), 99.4 (CH), 74.0 (CH_2), 20.7 (CH_2), 20.5 (Me), 20.2 (Me); HRMS calcd for $C_{15}H_{14}O_4$ + H 259.0965, found MH^+ 259.0964.

2-(*tert*-Butyldiphenylsiloxy)methylprop-2-en-1-ol. To sodium hydride (60% dispersion in mineral oil; 908 mg, 22.70 mmol) was added a solution of 2-methylenepropane-1,3-diol (2.00 g, 22.70 mmol) in dry THF (17.5 mL) under argon at 0 °C. After being stirred for 70 min at room temperature, the solution was cooled to 0 °C, and *tert*-butyldiphenylsilyl chloride (5.70 mL, 21.56 mmol) was added dropwise. The reaction mixture was stirred for 16 h at room temperature, the solvent was evaporated, and the residue was taken up in a mixture of water (20 mL) and ether (20 mL). The aqueous layer was extracted into ether (3 × 20 mL), and the combined organic layers were washed with brine (60 mL), dried over magnesium sulfate, and reduced in vacuo. The resulting oil was purified by flash chromatography (hexane/ethyl acetate, 9:1) to give the title compound (6.49 g, 88%) as a colorless oil (lit.[30] oil, bp not quoted): ν_{max} ($CHCl_3$)/cm^{-1} 3695, 3073, 3008, 2961, 2860, 1472, 1428, 1113, 824; δ_H (400 MHz; $CDCl_3$) 7.71−7.68 (4 H, m), 7.45−7.38 (6 H, m), 5.17−5.16 (1 H, m), 5.13−5.12 (1 H, m), 4.23 (2 H, s), 4.19 (2 H, d), 1.89−1.84 (1 H, br), 1.08 (9 H, s); δ_C (100 MHz; $CDCl_3$) 147.1 (C), 135.5 (CH), 133.2 (C), 129.8 (CH), 127.7 (CH), 111.1 (CH_2), 65.5 (CH_2), 64.5 (CH_2), 26.8 (Me), 19.2 (C); HRMS calcd for $C_{20}H_{26}O_2Si + Na^+$ 349.1594, found MNa^+ 349.1582.

3-Bromo-2-(*tert*-butyldiphenylsiloxy)methylpropene. To a solution of the above alcohol (2.0 g, 6.12 mmol) in ether (31 mL) at 0 °C was added phosphorus tribromide (0.70 mL, 7.35 mmol) dropwise under argon. The reaction mixture was stirred for 3 h at room temperature, and cold water (50 mL) was added slowly. The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and reduced in vacuo. The resulting colorless oil (1.84 g, 77%) was used without further

(30) Craig, D.; Henry, G. D. *Eur. J. Org. Chem.* **2006**, 3558.

purification (lit.[30] oil, bp not quoted): ν_{max} ($CHCl_3$)/cm^{-1} 3073, 3009, 2961, 2933, 2859, 1473, 1428, 1112, 825, 615; δ_H (400 MHz; $CDCl_3$) 7.71−7.69 (4 H, m), 7.47−7.38 (6 H, m), 5.32−5.30 (2 H, m), 4.32 (2 H, s), 4.04 (2 H, s), 1.08 (9 H, s); δ_C (100 MHz; $CDCl_3$) 144.4 (C), 135.5 (CH), 133.3 (C), 129.7 (CH), 127.7 (CH), 114.9 (CH_2), 64.2 (CH_2), 32.7 (CH_2), 26.8 (Me), 19.3 (C); HRMS calcd for $C_{20}H_{25}{}^{79}BrOSi + Na^+$ 411.0750, found MNa^+ 411.0758.

6-Allyl-7-[2-(*tert*-butyldiphenylsiloxy)methyl]allyloxy-5-hydroxy-2-methyl-4*H*-chromen-4-one 16. To a mixture of **14** (200 mg, 0.86 mmol) and the above bromide (894 mg, 1.72 mmol) in DMF (2.9 mL) was added potassium carbonate (262 mg, 1.89 mmol) at room temperature under argon. The reaction mixture was stirred for 20 h, diluted with ether (20 mL), and washed with saturated aqueous ammonium chloride (20 mL) and brine (2 × 20 mL). After the organic layer was dried over magnesium sulfate and reduced in vacuo, the resulting oil was purified by chromatography (light petroleum/ethyl acetate/ether, 8:1:1) to give the title compound (310 mg, 65%) as a colorless oil: ν_{max} ($CHCl_3$)/cm^{-1} 3007, 2932, 2859, 1660, 1625, 1591, 1490, 1452, 1343, 1186, 1113, 910; δ_H (400 MHz; $CDCl_3$) 12.83 (1 H, s), 7.70−7.67 (4 H, m), 7.44−7.36 (6 H, m), 6.38 (1 H, s), 6.04 (1 H, s), 5.85 (1 H, ddt, J = 17.1, 10.0, 6.2), 5.38 (1 H, s), 5.27 (1 H, s), 4.93 (1 H, ddt, J = 17.1, 1.9, 1.6), 4.86 (1 H, ddt, J = 10.0, 1.9, 1.4), 4.62 (2 H, s), 4.30 (2 H, s), 3.35 (2 H, d, J = 6.2), 2.33 (3 H, s), 1.10 (9 H, s); δ_C (100 MHz; $CDCl_3$) 182.4 (C), 166.4 (C), 161.8 (C), 158.6 (C), 156.6 (C), 142.7 (C), 135.7 (CH), 135.5 (CH), 133.2 (C), 129.8 (CH), 127.7 (CH), 114.5 (CH_2), 112.9 (CH_2), 111.0 (C), 108.8 (CH), 105.1 (C), 90.4 (CH), 68.9 (CH_2), 64.6 (CH_2), 26.8 (Me), 26.4 (CH_2), 20.4 (Me), 19.3 (C); HRMS calcd. for $C_{33}H_{36}O_5Si + Na^+$ 563.2224, found MNa^+ 563.2207.

8-(*tert*-Butyldiphenylsiloxy)methyl-5-hydroxy-2-methyl-6,9-dihydro-4*H*-oxepino[3,2-*g*]chromen-4-one. A mixture of diene **16** (60 mg, 0.11 mmol) and [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene](tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (Grubbs' II catalyst) (9.4 mg, 0.01 mmol) in dichloromethane (55 mL) was heated at 45 °C for 2 h under argon. The reaction mixture was evaporated in vacuo, and the resulting oil was purified by chromatography (light petroleum/ether, 75:25) to give the title compound (53 mg, 93%) as a colorless oil: ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3012, 2933, 2860, 1654, 1622, 1448, 1402, 1336, 1167, 1113, 851; δ_H (400 MHz; $CDCl_3$) 13.08 (1 H, s), 7.66−7.63 (4 H, m), 7.42−7.35 (6 H, m), 6.52 (1 H, s), 6.05 (1 H, s), 5.84 (1 H, t, J = 5.6), 4.71 (2 H, s), 4.07 (2 H, s), 3.53 (2 H, d, J = 5.6), 2.36 (3 H, s), 1.05 (9 H, s); δ_C (100 MHz; $CDCl_3$) 182.8 (C), 167.0 (C), 164.7 (C), 158.1 (C), 155.8 (C), 137.1 (C), 135.5 (CH), 133.2 (C), 129.7 (CH), 127.7 (CH), 123.5 (CH), 116.1 (C), 108.7 (CH), 106.6 (C), 99.2 (CH), 71.0 (CH_2), 66.2 (CH_2), 26.8 (Me), 21.0 (CH_2), 20.5 (Me), 19.2 (C); HRMS calcd for $C_{31}H_{32}O_5Si + Na^+$ 535.1911, found MNa^+ 535.1891.

5-Hydroxy-8-hydroxymethyl-2-methyl-6,9-dihydro-4*H*-oxepino-[3,2-*g*]chromen-4-one (Ptaeroxylinol, 9). To a solution of the above silyl ether (39 mg, 0.076 mmol) in THF (0.4 mL) was added tetra-*n*-butylammonium fluoride solution (1 M in THF; 84 μL, 0.084 mmol) dropwise at 0 °C under argon. After 1 h at 5 °C, the mixture was diluted with ethyl acetate (3 mL) and washed with a saturated aqueous ammonium chloride solution (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulfate and evaporated in vacuo, and the resulting oil was purified by chromatography (light petroleum/ethyl acetate, 1:1) to give the title compound (13 mg, 65%) as colorless crystals: mp 140−142 °C (lit.[16] mp 135 °C; lit.[28] mp 145 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3605, 3009, 2928, 1655, 1627, 1594, 1449, 1407, 1274, 1157, 1083, 850; δ_H (400 MHz; $CDCl_3$) 13.06 (1 H, s), 6.51 (1 H, s), 6.03 (1 H, s), 5.99 (1 H, t, J = 5.0), 4.74 (2 H, s), 4.04 (2 H, d, J = 5.4), 3.57 (2 H, d, J = 5.0), 2.35 (3 H, s), 1.51 (1 H, t, J = 5.4); δ_C (100 MHz; $CDCl_3$) 182.8 (C), 167.2 (C), 164.6 (C), 158.1 (C), 155.8 (C), 138.0 (C), 125.3 (CH), 115.8 (C), 108.7 (CH), 106.6 (C), 99.3 (CH), 71.0 (CH_2), 65.7 (CH_2), 21.1 (CH_2), 20.5 (Me); HRMS calcd for $C_{15}H_{14}O_5 + Na^+$ 297.0733, found MNa^+ 297.0736.

7-Allyloxy-5-hydroxy-2-methyl-4*H*-chromen-4-one (17). To a solution of noreugenin (**11**) (500 mg, 2.60 mmol) in DMF (26 mL) was added potassium carbonate (791 mg, 5.73 mmol), followed by allyl bromide (0.5 mL, 5.73 mmol) at room temperature under argon. After 3 h, the reaction mixture was filtered and washed with a saturated aqueous ammonium chloride solution (25 mL). The resulting mixture was extracted into ethyl acetate (2 × 25 mL), and the combined organic fractions were washed with brine (2 × 25 mL), dried over magnesium sulfate, and evaporated in vacuo. The residue was taken up in ethyl acetate (2 mL), and light petroleum was added to precipitate the product. Filtration afforded the title compound (243 mg, 40%) as a beige solid: mp 109−110 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3009, 1664, 1626, 1591, 1505, 1417, 1388, 1342, 1267, 1166, 1114, 1078, 1028, 849; δ_H (400 MHz; $CDCl_3$) 12.68 (1 H, s), 6.35 (1 H, d, J = 2.3), 6.33 (1 H, d, J = 2.3), 6.03 (1 H, ddt, J = 17.3, 10.5, 5.3), 6.00 (1 H, s), 5.42 (1 H, ddt, J = 17.3, 1.5, 1.4), 5.32 (1 H, ddt, J = 10.5, 1.4, 1.3), 4.57 (2 H, dt, J = 5.3, 1.5), 2.33 (3 H, s); δ_C (100 MHz; $CDCl_3$) 182.4 (C), 166.8 (C), 164.2 (C), 162.1 (C), 158.0 (C), 132.1 (CH), 118.4 (CH_2), 108.7 (CH), 105.2 (C), 98.5 (C), 93.1 (CH), 69.1 (CH_2), 20.5 (Me); HRMS calcd for $C_{13}H_{12}O_4 + Na^+$ 255.0628, found MNa^+ 255.0622.

8-Allyl-7-[2-(*tert*-butyldiphenylsiloxy)methyl]allyloxy-5-hydroxy-2-methyl-4*H*-chromen-4-one (19). A solution of allyl ether **17** (166 mg, 0.72 mmol) in DMF (12 mL) was heated at 220 °C for 90 min in a microwave reactor (300 W). The solvent was evaporated, and light petroleum/ethyl acetate (8:2) (50 mL) was added to the resulting oil. After filtration through a short pad of silica gel and evaporation of the filtrate, the resulting solid was added to allylic bromide (583 mg, 1.50 mmol) and the mixture was dissolved in DMF (2.3 mL). Potassium carbonate (207 mg, 1.50 mmol) was added, and the mixture was stirred for 5 h at room temperature under argon. The reaction mixture was filtered, diluted with ethyl acetate (3 mL), and washed with a saturated aqueous ammonium chloride solution (3 mL) and brine (5 mL). The organic fraction was dried over magnesium sulfate and evaporated in vacuo, and the resulting oil was purified by chromatography (light petroleum/ethyl acetate, 9:1) to give the title compound (171 mg, 45%) and the regioisomer **16** (45 mg, 18%) (data given previously) as colorless oils: ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3009, 2932, 2859, 1660, 1620, 1592, 1427, 1387, 1327, 1269, 1192, 1113, 848; δ_H (400 MHz; $CDCl_3$) 12.78 (1 H, s), 7.69−7.66 (4 H, m), 7.43−7.38 (6 H, m), 6.35 (1 H, s), 6.02 (1 H, s), 5.77 (1 H, ddt, J = 17.0, 10.0, 6.2), 5.39 (1 H, s), 5.27 (1 H, s), 4.89 (1 H, dd, J = 17.0, 1.8), 4.85 (1 H, dd, J = 10.0, 1.8), 4.59 (2 H, s), 4.28 (2 H, s), 3.37 (2 H, d, J = 6.2), 2.35 (3 H, s), 1.08 (9 H, s); δ_C (100 MHz; $CDCl_3$) 182.9 (C), 166.7 (C), 161.6 (C), 160.7 (C), 154.9 (C), 142.8 (C), 135.7 (CH), 135.5 (CH), 133.3 (C), 129.7 (CH), 127.7 (CH), 114.6 (CH_2), 112.8 (CH_2), 108.3 (CH), 105.9 (C), 104.8 (C), 95.9 (CH), 69.2 (CH_2), 64.5 (CH_2), 26.8 (Me), 26.7 (CH_2), 20.5 (Me), 19.3 (C); HRMS calcd for $C_{33}H_{36}O_5Si + H^+$ 541.2405, found MH^+ 541.2384.

9-(*tert*-Butyldiphenylsilyloxy)methyl-5-hydroxy-2-methyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one. To a solution of diene **19** (68 mg, 0.126 mmol) in distilled dichloromethane (63 mL) was added [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (Grubbs' II catalyst) (11 mg, 0.013) in one portion under argon. The reaction mixture was heated at 45 °C for 2.5 h and evaporated after cooling. The resulting oil was purified by chromatography (light petroleum/ether, 7:3) to give the stating material (14 mg) and the title compound (50 mg, 98% based on recovered starting material) as a colorless oil: ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 2932, 2859, 1660, 1598, 1488, 1419, 1269, 1189, 1159, 1105,

850; δ_H (400 MHz; $CDCl_3$) 12.65 (1 H, s), 7.66−7.63 (4 H, m), 7.42−7.36 (6 H, m), 6.47 (1 H, s), 6.07 (1 H, s), 5.86 (1 H, tt, J = 5.7, 1.2), 4.68 (2 H, d, J = 1.2), 4.07 (2 H, s), 3.58 (2 H, d, J = 5.7), 2.39 (3 H, s), 1.05 (9 H, s); δ_C (100 MHz; $CDCl_3$) 183.1 (C), 166.7 (C), 164.5 (C), 160.1 (C), 153.8 (C), 137.8 (C), 135.5 (CH), 133.2 (C), 129.7 (CH), 127.7 (CH), 122.4 (CH), 111.2 (C), 108.7 (CH), 107.0 (C), 104.6 (C), 70.7 (CH_2), 66.0 (CH_2), 26.8 (Me), 21.4 (CH_2), 20.5 (Me), 19.2 (C); HRMS calcd for $C_{31}H_{32}O_5Si + H^+$ 513.2092, found MH^+ 513.2070.

5-Hydroxy-9-(hydroxymethyl)-2-methyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (Eranthin, 10). To a solution of the above silyl ether (40 mg, 0.078 mmol) in THF (0.4 mL) was added tetra-*n*-butylammonium fluoride solution (1 M in THF; 86 μL, 0.086 mmol) dropwise at 0 °C under argon. After 1 h at 5 °C, the mixture was diluted with ethyl acetate (3 mL) and washed with a saturated aqueous ammonium chloride solution (3 mL) and brine (3 mL). The organic layer was dried over magnesium sulfate and evaporated in vacuo, and the resulting oil was purified by chromatography (dichloromethane/methanol, 97:3) to give the title compound (18 mg, 86%) as colorless crystals: mp 160−161 °C (lit.[17] mp 160−161.5 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3606, 3008, 2930, 1660, 1620, 1595, 1488, 1419, 1394, 1269, 1180, 1159, 1104, 1074, 851; δ_H (400 MHz; $CDCl_3$) 12.58 (1 H, s), 6.43 (1 H, s), 6.03 (1 H, s), 5.98 (1 H, tt, J = 5.7, 1.1), 4.72 (2 H, d, J = 1.1), 4.03 (2 H, s), 3.60 (2 H, d, J = 5.7), 2.37 (3 H, s), 1.78 (1 H, s); δ_C (100 MHz; $CDCl_3$) 183.0 (C), 166.9 (C), 164.4 (C), 160.0 (C), 153.7 (C), 138.5 (C), 124.3 (CH), 110.9 (C), 108.7 (CH), 106.9 (C), 104.5 (CH), 70.7 (CH_2), 65.4 (CH_2), 21.4 (CH_2), 20.5 (Me); HRMS calcd for $C_{15}H_{14}O_5 + Na^+$ 297.0733, found MNa^+ 297.0724.

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Supporting Information Available: General experimental details, ORTEP pictures for X-ray crystal structures of compounds **9** and **10**, copies of ^1H and ^{13}C NMR spectra, and X-ray data for compounds **9** and **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.